

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

THIS PAGE BLANK (USPTO)



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: A61L 29/00, A61L 31/00	A1	(11) International Publication Number: WO 00/18446 (43) International Publication Date: 06 April 2000 (06.04.2000)
(21) International Application Number: PCT/EP99/07156 (22) International Filing Date: 27 September 1999 (27.09.1999) (30) Priority Data: 98402367.1 25 September 1998 (25.09.1998) EP (60) Parent Application or Grant LABORATOIRES NYCOMED S.A. [/]; (). BESSIERE, Fabienne [/]; (). STROHBAND, Hans-Peter [/]; (). ANDERSEN, Erik [/]; (). BESSIERE, Fabienne [/]; (). STROHBAND, Hans-Peter [/]; (). ANDERSEN, Erik [/]; (). BOYDELL, John, Christopher ; ().	Published	
(54) Title: MULTI-LAYERED SLEEVE FOR INTRAVASCULAR EXPANDABLE DEVICE (54) Titre: MANCHON MULTICOUCHE POUR DISPOSITIF INTRAVASCULAIRE EXPANSIBLE (57) Abstract <p>The present invention relates to a multi-layered sleeve for encompassing an expandable device to be introduced into a body canal, such as a blood vessel for example. More particularly, the present invention relates to a therapeutic agent-releasing multi-layered sleeve (1, 2) for encompassing an expandable device (3), such as a stent, to be introduced into a body canal, such as a blood vessel for example. Hence, the present invention is primarily applicable to the treatment of disorders of body canals comprising a canal wall and a lumen through which a body fluid flows. Examples of such body canals are the oesophagus, the urethra, and the coronary and peripheral blood vessels.</p> (57) Abrégé <p>La présente invention concerne un manchon multicouche destiné à envelopper un dispositif expansible devant être introduit dans un canal du corps, tel qu'un vaisseau sanguin par exemple. Plus particulièrement, la présente invention concerne un manchon (1, 2) multicouche de libération d'agents thérapeutiques destiné à envelopper un dispositif (3) expansible tel qu'une prothèse endovasculaire devant être introduit dans un canal du corps, tel qu'un vaisseau sanguin par exemple. Ainsi, la présente invention peut être d'abord appliquée au traitement de troubles dans des canaux du corps comprenant une paroi de canal et une lumière par laquelle s'écoule un fluide corporel. L'oesophage, l'urètre, et les vaisseaux sanguins coronaires et périphériques constituent des exemples de ces canaux du corps.</p>		

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61L 29/00, 31/00		A1	(11) International Publication Number: WO 00/18446
			(43) International Publication Date: 6 April 2000 (06.04.00)
(21) International Application Number: PCT/EP99/07156		(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(22) International Filing Date: 27 September 1999 (27.09.99)			
(30) Priority Data: 98402367.1 25 September 1998 (25.09.98) EP		Published With international search report.	
(71) Applicant (for all designated States except US): LABORA-TOIRES NYCOMED S.A. (FR/FR); Centre d'Affaires et d'Activites, "Tolbiac Massena", 25, quai Panhard Levas-sor, F-75013 Paris (FR).			
(72) Inventors; and (75) Inventors/Applicants (for US only): BESSIERE, Fabienne [FR/FR]; 1, avenue Gallieni, F-94100 Saint Maur (FR). STROHBAND, Hans-Peter [DE/DE]; Carl Zuckmayer Strasse 32, D-40699 Erkrath (DE). ANDERSEN, Erik [DK/DK]; Ronnens Kut 5, DK-4000 Osted Roskilde (DK).			
(74) Agents: BOYDELL, John, Christopher et al.; Stevens Hewlett & Perkins, 1 Serjeants' Inn, Fleet Street, London, Greater London EC4Y 1NT (GB).			
(54) Title: MULTI-LAYERED SLEEVE FOR INTRAVASCULAR EXPANDABLE DEVICE			
(57) Abstract <p>The present invention relates to a multi-layered sleeve for encompassing an expandable device to be introduced into a body canal, such as a blood vessel for example. More particularly, the present invention relates to a therapeutic agent-releasing multi-layered sleeve (1, 2) for encompassing an expandable device (3), such as a stent, to be introduced into a body canal, such as a blood vessel for example. Hence, the present invention is primarily applicable to the treatment of disorders of body canals comprising a canal wall and a lumen through which a body fluid flows. Examples of such body canals are the oesophagus, the urethra, and the coronary and peripheral blood vessels.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroun	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

Description

5

10

15

20

25

30

35

40

45

50

55

5

MULTI-LAYERED SLEEVE FOR INTRAVASCULAR EXPANDABLE DEVICE

10

The present invention relates to a multi-layered sleeve for
5 encompassing an expandable device to be introduced into a body canal,
15 such as a blood vessel for example and to a method of manufacturing such
a sleeve.

More particularly, the present invention relates to a therapeutic
20 agent-releasing multi-layered sleeve for encompassing an expandable
10 device, such as a stent, to be introduced into a body canal, such as a
blood vessel for example.

Hence, the present invention is primarily applicable to the treatment
25 of disorders of body canals comprising a canal wall and a lumen through
which a body fluid flows. Examples of such body canals are the
15 oesophagus, the urethra, and the coronary and peripheral blood vessels.

Disorders of body canals, such as coronary arteries for example, are
30 generally caused or provoked by the presence, on the inner walls of the
canal, of deposits which cause strictures or stenoses in said canal.

The treatment of such disorders generally calls for the use of an
35 20 inflatable device, such as a dilatation catheter for example, for restoring the
normal section of flow of the canal at the level of the stenosis. In a certain
number of cases, the result is further optimised through implantation of an
40 expandable device in order to provide support to the vessel wall.

Such expandable devices are well-known in the field of medicine for
25 25 implantation in blood vessels, biliary ducts, or indeed other similar organs
of the living body. They generally fall into two categories: those known as
45 self-expandable prostheses, and those which require a forced expansion
with the aid of a balloon for example; both types are commonly known as
stents in the cardiovascular field. Such expandable devices are used to
50 30 maintain, open, or dilate tubular structures or to support tubular structures

CONFIRMATION COPY

55

5

2

that are being anastomosed.

10

Although stents have in general shown to be very effective in restoring canal patency by virtue of a scaffolding role which counteracts the phenomenon of remodelling, the implantation of a stent provokes substantial vascular injury which in some cases leads to clinical symptoms and the necessity for medical reintervention. Subacute stent thrombosis remains a threat post-stent implantation in spite of improvements in drug regimens applied post-intervention. More importantly, the healing response of the arterial wall post implantation engenders the proliferation of smooth muscle cells and consequently the formation of neointimal hyperplasia which leads to inner stent-restenosis, a condition for which no satisfactory solution has yet been found.

25

Methods of inhibiting thrombus formation has been the subject of much research and publications in the literature. The object of the majority of this research has been into coated stents.

30

One of the methods described uses the concept of coating a stent with a polymer. Furthermore, the local delivery of therapeutic agent(s) using stents has centred around two concepts :

35

i) directly coating the stent wires with a therapeutic agent or a therapeutic agent-polymer combination (Bailey *et al.*, Circulation, 1990, 82: III-541 ; Cavendar *et al.*, Circulation, 1990, 82 :III-541) ; and

40

ii) incorporating a therapeutic agent into a stent that was constructed not of metal but of a biodegradable polymer (Murphy *et al.*, J. Invasive Cardiol., 1991, 3 : 144-148).

45

The major advantage of directly coating a device, such as a stent wire, with a therapeutic agent or a therapeutic agent-polymer combination is the low quantity of therapeutic agent necessary because the therapeutic agent is released close to the indwelling device.

50

Most efforts were focused upon directly coating the metal stent wires with a polymer. This polymer is usually placed directly on the stent

55

5

3

10

15

20

25

30

35

40

45

50

55

(for example by the method disclosed in EP-A-0 797 963, which involves dipping the stent in a solution of a polymer in a solvent, followed then by the evaporation of the solvent) or is covalently bound to the metal. The polymer is bonded to or contains an anticoagulant compound. Most coated stents currently under development use heparin as the active ingredient. One of the more effective polymer coated stent is Biogold (van der Giessen *et al.*, Circulation, 1990, 82 :III-542). Biogold and other coated stents have not however completely prevented arterial thrombosis. This is probably due to the cracking of the polymer as the stent is expanded during deployment, saturation of the anticoagulant binding sites on the stent, and/or the inadequacy of heparin as an anticoagulant in the prevention of arterial thrombosis and/or too small quantities of therapeutic agent in comparison with the total surface of arteries wall covered by the stent. It is because of these inadequacies associated with polymer coatings directly applied to stent wires that there remains a great need to effectively prevent vascular response at the site of the stent.

US 5,383,928 (EMORY UNIVERSITY, United States of America) entitled "Stent sheath for local therapeutic agent delivery" discloses a stent sheath for local therapeutic agent delivery. More specifically, the patent discloses a sheath for encompassing at least a portion of a stent to locally deliver a drug to an arterial wall or lumen into which the stent has been inserted, comprising a polymer and a drug incorporated within the polymer, the polymer sheath encompassing at least a portion of the stent and having a thickness to allow controlled release of the drug.

The major disadvantage of the sheath according to this prior art document resides in the fact that in order to change the therapeutic agent or adapt the therapeutic agent release rate incorporated therein, it is necessary to change the entire sheath itself (thickness, nature of polymer(s) etc.). Consequently, the whole mechanical properties of the entire sheath would also be changed.

5

4

10

The principal aim of the present invention therefore is to solve the technical problem consisting in providing a sleeve for encompassing an expandable device for introduction into a body canal of a patient, said sleeve being adaptable in every way to the needs of the patient's canal in question.

15

More specifically, in order for said sleeve to be adaptable in every way to the needs of the patient's canal in question, the sleeve, preferably of polymeric nature, would have to meet the following requirements in being :

20

10 (a) bio-compatible, it causing little or no response from the body canal in question;

25

(b) non-biodegradable, it being required to remain without any change in its properties in contact with the body canal in question for a specified amount of time;

30

15 (c) sufficiently elastic to be expandable, when wet with a body fluid for example, it being capable of being expanded to the dimensions of the body canal in question; but,

35

(d) sufficiently inelastic so as not to recoil from its expanded state;

(e) of a sufficient mechanical strength so as it tears neither under expansion nor in the expanded state;

40

(f) of such a chemical nature that it is optionally able not only to be either coated or impregnated with any therapeutic agent(s) whatsoever in need of which the patient's body canal in question may be, said therapeutic agent(s) being capable of treating either a disorder of a body fluid flowing through the patient's body canal or a disorder of a body canal wall, or, more importantly, both, but furthermore of such a chemical nature that the rate of release of said therapeutic agent(s) be controlled at a rate pre-determinable according to the needs of the patient's body canal in question,

50

30 (g) in the case where the therapeutic agent(s) are impregnated in

55

5

5

10

the sleeve, the sleeve would have to be of a thickness pre-determinable according to the amount of therapeutic agent(s) it is desired to be released i.e. the thicker the sleeve, the more therapeutic agent(s) it may contain and release, and, finally,

15

5 (h) able to optionally encompass an expandable device, a stent for example, it being possible for said expandable device to be either embedded within said sleeve, or disposed radially and internally with respect to said sleeve, according to the needs of the patient.

20

The inventors of the present invention have carefully addressed the above-mentioned requirements and have been able to provide a solution to the present technical problem in the form of a sleeve which is comprised not of just a mixture of polymers, but a system of polymer layers.

25

30

More importantly, the sleeve in accordance with the present invention is comprised of a system of polymer layers which are actually able to adhere together without affecting the elasticity and mechanical properties of the sleeve resulting therefrom in any way whatsoever, and which thus provides a solution to the present technical problem in the form of a sleeve having highly advantageous properties over those of the prior art in a totally unexpected way.

35

40

20 Thus, according to a first aspect, the present invention provides a sleeve for encompassing an expandable device for introduction into a body canal, characterised in that said sleeve is multi-layered and comprises at least one biocompatible, non-biodegradable elastic polymer layer onto which one synthetic hydrogel inner layer and/or one synthetic hydrogel outer layer is bound, said hydrogel inner layer being optionally different from said hydrogel outer layer, the nature and thickness of said biocompatible, non-biodegradable elastic layer being such that predetermined mechanical properties of said sleeve be provided.

45

50

According to a second principal aspect, the present invention provides a sleeve for encompassing an expandable device for introduction

55

5

6

10

15

20

25

30

35

40

45

50

55

into a body canal, characterised in that said sleeve is multi-layered and comprises at least one biocompatible, non-biodegradable elastic polymer layer onto which at least one synthetic therapeutic agent(s)-containing hydrogel inner layer and/or at least one synthetic therapeutic agent(s)-containing hydrogel outer layer is bound, said therapeutic agent(s)-containing hydrogel inner layer being optionally different from said therapeutic agent(s)-containing hydrogel outer layer, the nature and thickness of said biocompatible, non-biodegradable elastic polymer layer being such that predetermined mechanical properties of said sleeve be provided, and the nature and thickness of said therapeutic agent(s)-containing hydrogel inner and outer layers being such that a pre-determined rate of release of said therapeutic agent(s) be controlled.

Advantageously, the mechanical properties of the resulting sleeve are thus governed by the at least one biocompatible, non-biodegradable elastic polymer layer, and the excellent biocompatibility of said sleeve are conferred thereto by the hydrogel inner and/or outer layers. Moreover, said sleeve, when wet with body fluid at 37°C is able to expand according to the needs of the patient's body canal, this being without any unsticking of the layers comprising said sleeve.

Within the context of the present invention the term:

"non-biodegradable" is understood as meaning a polymer which does not fail the "environmental stress cracking", or "ESC". ESC has been attributed to biochemical and cellular interactions at the surface of the implanted material causing polymer chain cleavage. This may result in surface fissuring followed by deep cracking associated with considerable biodegradation of the polymer, resulting in loss of mechanical strength;

"biocompatible" is as defined by the US Pharmacopeia and refers to a polymer which successfully passes the USP Class VI plastics testing; and

"hydrogel" is understood as meaning a material which is hydrophilic

5

7

10

15

20

25

30

35

40

45

50

55

in nature and which exhibits the characteristic macromolecular structure of a gel. A gel is best described as a continuous three-dimensional network that is held together by chemical or physical bonds. Sufficient interstitial space exists within the network, and water molecules can become trapped and immobilised, filling the available free volume. Gels can be divided into two major categories based on the types of bonds that comprise them. These include chemical gels and physical gels.

Advantageously, the above-mentioned sleeve is characterised in that said biocompatible, non-biodegradable elastic polymer layer comprises a material selected from the group consisting of polyurethane, silicone, and latex. The material needs to have a good elasticity that is an elongation of at least 500% (PU tensile strength 7,500 psi elongation 500%, latex tensile strength 85 kg/cm² elongation 700%, silicone tensile strength 1310, elongation 1000%) and a good flexure resistance in vivo (no oxidation of the material even if the sleeve is stretched).

The nature of the hydrogel and the appropriate thickness of a layer or film containing same shall be easily determined by the person skilled in the art in taking into consideration the specific nature of the therapeutic agent(s) to be released therefrom.

Also advantageously, the above-mentioned sleeve is characterised in that said hydrogel outer and inner layers independently comprise at least one hydrophilic polymer selected from the group consisting of polyhydroxyethyl methacrylate, polyvinyl alcohol, polyacrylamide, poly(N-vinylpyrrolidone), polyethylene oxide, hydrolysed polyacrylonitrile, polyacrylic acid, polymethacrylic acid, polyethylene amine, alginic acid, pectinic acid, carboxy methyl cellulose, and hyaluronic acid.

Such hydrophilic polymers are particularly preferred within the context of the present invention because they possess a capacity to act as a vehicle for the therapeutic agent(s) useful for treating a body canal, and, more importantly, because they are able, once mixed with other polymers

5

8

10

or cross-linked, to release the therapeutic agent(s) at a rate which is pre-determinable by easy selection of the thickness of said film or layer, and the ratio of therapeutic agent with the hydrogel.

15

The nature of the composition of the hydrogel and the appropriate thickness of a layer or film containing same shall be easily determined by the person skilled in the art in taking into consideration the specific nature of the therapeutic agent(s) to be released therefrom.

20

An example of a particularly preferred hydrophilic polymer that may be used within the context of the present invention is poly (N-vinylpyrrolidone), especially when the biocompatible, non-biodegradable elastic polymer layer is made of polyurethane. A particularly suitable material is produced under the trade name Hydromer and is made by the interaction of poly-vinylpyrrolidone (PVP) with one of several isocyanate prepolymers.

25

30

According to an advantageous embodiment of the present invention, the above-mentioned sleeve is characterised in that said therapeutic agent(s)-containing hydrogel inner layer contains one or more therapeutic agents capable of treating a disorder of a body fluid.

35

According to a further advantageous embodiment of the present invention, the above mentioned sleeve is characterised in that said therapeutic agent(s)-containing hydrogel outer layer contains one or more therapeutic agents capable of treating a disorder of a body canal wall.

40

Within the context of the present invention, the term "therapeutic agent" is understood as meaning any compound which has a pharmacological effect.

45

Particularly advantageously, the above-mentioned sleeve is characterised in that said therapeutic agent(s) is (are) selected from the group consisting of an anticoagulant, such as D-Phe-Pro-Arg chloromethyl ketone, an RGD peptide-containing compound, heparin, an antithrombin compound, a platelet receptor antagonist, an anti-thrombin antibody, an

50

55

5 anti-platelet receptor antibody, aspirin, a prostaglandin inhibitor, a platelet
10 inhibitor, a tick anti-platelet peptide, or a combination thereof ; a promoter
of vascular cell growth, such as a growth factor stimulator, a growth factor
receptor antagonist, a transcriptional activator, a translational promoter, or
15 a combination thereof ; an inhibitor of vascular cell growth, such as a
growth factor inhibitor, a growth factor receptor antagonist, a transcriptional
repressor, a translational repressor, an antisense DNA, an antisense RNA,
20 a replication inhibitor, an inhibitory antibody, an antibody directed against
growth factors, a bifunctional molecule consisting of a growth factor and a
10 cytotoxin, and a bifunctional molecule consisting of an antibody and a
cytotoxin, or a combination thereof ; a cholesterol-lowering agent, a
25 vasodilating agent, an agent which interferes with endogenous vasoactive
mechanisms, or a combination thereof ; or a smooth muscle inhibitor, such
as an agent which modulates intracellular calcium binding proteins, a
15 receptor blocker for contractile agonists, an inhibitor of the
sodium/hydrogen antiporter, a protease inhibitor, a nitrovasodilator, a
30 phosphodiesterase inhibitor, a phenothiazine, a growth factor receptor
agonist, an antimitotic agent, an immunosuppressive agent, a protein kinase
inhibitor, or a combination thereof ; or a combination thereof.

20 According to a third principal aspect, the present invention provides
a system for introduction into a body canal, characterised in that it
comprises an expandable device and a multi-layered sleeve in accordance
40 with the present invention.

According to an advantageous variant, the present invention
25 provides a system which is characterised in that said expandable device
for introduction into a body canal is embedded within said biocompatible,
45 non-biodegradable elastic polymer layer.

According to a further advantageous variant, the present invention
provides a system which is characterised in that said expandable device
50 30 for introduction into a body canal is disposed radially and internally with

5

10

respect to said hydrogel inner layer.

10

According to a particularly advantageous variant, the present invention provides a system which is characterised in that said expandable device for introduction into a body canal is a stent.

15

5 The sleeve length may be of shorter or longer length than the expandable device optionally encompassed therein, or of course be of the same length.

20

According to a fourth aspect, the present invention provides a system which is characterised in that it is intended to be introduced into a body canal comprising a canal wall and a lumen through which a body fluid flows and in that said sleeve comprises a hydrogel inner layer which can contain one or more therapeutic agents capable of treating a disorder of said body fluid, and a hydrogel outer layer which can contain one or more therapeutic agents capable of treating a disorder of said body canal wall.

25

30

15 According to a fifth aspect a particularly advantageous method of manufacturing the sleeve of the invention comprises dipping a mandrel successively into different solutions in order to build up said layers, said dipped mandrel being subject to curing inbetween each successive dipping.

35

20 Various alternative methods of manufacture are described in more detail below in the Examples.

40

The invention will be better understood and other objects, characteristics and advantages thereof will become more clearly apparent from the following explanatory description referring to the attached schematic drawings, which are given solely by way of non-limiting examples illustrating two preferred embodiments of the invention, and in which:

45

25 Figure 1 is a longitudinal schematic view showing a system comprising a stent and a multi-layered sleeve according to a first preferred embodiment of the invention, in which said stent is disposed radially and

50

30

55

internally with respect to said multi-layered sleeve, represented in a body canal;

Figure 1A is a view in cross section of Figure 1;

Figure 2 is a longitudinal schematic view, similar to Figure 1, illustrating a second preferred embodiment of the sleeve according to the invention, in which the stent is embedded within the biocompatible, nonbiodegradable elastic polymer inner layer of said sleeve;

Figure 2A is a view in cross section of Figure 2.

In all Figures 1A, 1B, 2A, and 2B,

1 represents the at least one, optionally therapeutic agent(s)-containing, hydrogel outer layer of the multi-layered sleeve in accordance with the present invention,

2 represents the at least one biocompatible, non-biodegradable elastic polymer layer of the multi-layered sleeve in accordance with the present invention,

3 represents the expandable device for introduction into a body canal; and

4 represents at least one, optionally therapeutic agent(s)-containing, hydrogel inner layer of the multi-layered sleeve in accordance with the present invention.

The multi-layered sleeve is advantageously manufactured by a dipping process in which a mandrel is successively dipped in a solution in which there are different components, polymers and solvents. This successive dipping process builds up the different layers of the sleeve, as detailed above, and also ensures that, should an expandable device such as a stent be incorporated, such a device may, if required, be fully embedded in the finished sleeve. Layers which are required to be thicker than one dipping can provide are made by multiple dippings of the same component until the required thickness has been built up. Each dipping step consists in vertically immersing the mandrel in the different solutions

5

12

using an automatic soaking machine. The thickness of membrane laid
down at each dipping step is controlled by the following parameters:

10

the rate of insertion into the solution;

the time resident in the solution;

15

the rate of withdrawal from the solution;

the concentration of the solution.

After each dipping step, the coated mandrel is subject to curing.

During curing the following phenomena occur:

20

Cross-linking of the principal components.

10

Solvent evaporation.

It is important to ensure that the cross-linking is complete and that
all of the solvent has been evaporated from the different layers. To ensure
this, the temperature at which the curing takes place, and the duration of
curing, may be controlled. At the completion of the processing, the sleeve
is removed from the mandrel.

25

15

30

The following examples give detail of the technique which is
followed, it being understood that these are provided as an illustration of
the technique used to prepare the sleeves according to the present
invention and are in no way intended to limit the scope of the invention.

35

20

EXAMPLE I:

PREPARATION OF A SLEEVE WITH A HEPARIN-CONTAINING HYDROGEL INNER LAYER

40

A 10% solution of polyurethane in N,N-dimethylacetamide is
prepared. A 1.25 mm mandrel is dipped in the solution. The dipped
mandrel is cured at 75°C in an oven for 20 minutes.

45

The mandrel is dipped again in the solution. The mandrel is cured
again at 75°C for 20 minutes. The mandrel is then dipped in the hydrophilic
solution containing the heparin (3% of heparin benzalkonium chloride
solution + PVP) and is then cured at 60°C for 30 minutes. The sheath is

50

30

55

5

13

10

retrieved from the mandrel and reversed (i.e. turned inside out, or transposed). The membrane is inserted onto a transluminal prosthesis (stent).

15

The transluminal prosthesis is placed onto a 3.5 PTCA catheter and is inflated at the 3.5 mm diameter.

The transluminal prostheses are then tested for anti-clotting properties in comparison with the transluminal prosthesis without the hydrogel inner layer.

20

The inner surfaces were then extracted in human plasma at 37°C for 7, 10, 21 or 28 days and then tested for anti-clotting properties. The results obtained are shown in the Table.

25

TABLE

SAMPLE	CLOTTING TIME (minutes)
Uncoated sample	12
coated sample without extraction of plasma	did not clot
coated sample with 7 days extraction in plasma	did not clot
coated sample with 10 days extraction in plasma	did not clot
coated sample with 21 days extraction in plasma	24
coated sample with 28 days extraction in plasma	20

30

35

40

15

EXAMPLE 2:

45

PREPARATION OF A SLEEVE WITH THE SAME HYDROGEL INNER AND OUTER LAYERS

50

A 7% solution of polyurethane in N,N-dimethylacetamide is prepared.

A hydrophilic solution is prepared as follows:

55

5

14

10

polyvinylpyrrolidone 1 g
nitrocellulose 0.12 g
ethanol 9 ml
dimethylformamide 3.0 ml
ethyl acetate 0.4 ml

15

5

A 1.25 mm diameter mandrel is dipped in the polyurethane solution.

20

The dipped mandrel is cured at 75°C in an oven for 20 minutes. The mandrel is dipped again in the polyurethane solution, and cured again at 75°C for 20 minutes. The mandrel is then dipped again in the hydrophilic solution and cured for 30 minutes at 75°C.

10

25

The sleeve is retrieved from the mandrel, reversed and put again onto the mandrel.

The mandrel is dipped again in the hydrophilic solution and cured for 30 minutes at 75°C.

30

15

The sleeve is retrieved from the mandrel, cut and inserted onto a transluminal prosthesis (stent).

The transluminal prosthesis is placed onto 2-4 PTCA catheter and is inflated at the 2-4 mm diameter.

35

20

EXAMPLE 3: PREPARATION OF STENT INCLUDING SLEEVE WITH THE SAME HYDROGEL INNER AND OUTER LAYERS (According to Figure 2)

40

A 10% solution of polyurethane in N,N-dimethylacetamide is prepared.

45

25

A 1 mm diameter mandrel is dipped in the solution. The dipped mandrel is cured at 75°C in an oven for 20 minutes. The mandrel is then dipped in the hydrophilic solution (7.5% PVP solution) and is then cured at 75°C for 30 minutes.

50

The sleeve is retrieved from the mandrel, reversed and put back on the mandrel.

30

55

5

15

10

The transluminal prothesis (stent) is put onto the mandrel and the sleeve and is crimped on it.

The mandrel is dipped again in the polyurethane solution. The mandrel is cured again at 75°C for 20 minutes.

15

5 The mandrel is then dipped in the hydrophilic solution (7.5% PVP solution) and is then cured at 75°C for 30 minutes.

20

The transluminal prothesis is placed onto 2-4 PTCA catheter and is inflated at the 2-4 mm diameter.

10 EXAMPLE 4:

PREPARATION OF A SLEEVE WITH HYDROGEL OUTER LAYER

25

A 7% solution of polyurethane in N,N-dimethylacetamide is prepared.

A hydrophilic solution is prepared as follows:

30

15 polyvinylpyrrolidone 1 g
nitrocellulose 0.12 g
ethanol 9 ml
dimethylformamide 3.0 ml
ethyl acetate 0.4 ml

35

20 Two mandrels (A and B) of 1.25 mm in diameter are dipped in the polyurethane solution. The dipped mandrels are cured at 75°C in an oven for 20 minutes. The mandrels are dipped again in the polyurethane solution, and cured again at 75°C for 20 minutes. The mandrel A is then dipped in the hydrophilic solution and cured for 30 minutes at 75°C.

40

45

25 The sleeve is retrieved from the mandrels. A tensile test is done on the two wet sleeves at 37°C. The two curves are identical up to 1000% elongation.

50

55

5

16

EXAMPLE 5:

10

PREPARATION OF A SLEEVE WITH HYDROGEL INNER AND OUTER LAYERS

15

A 18% solution of polyurethane in N,N-dimethylacetamide is prepared. A 2 mm, mandrel is dipped in a first hydrogel solution.

The dipped mandrel is cured at 70°C in an oven for 60 minutes.

20

The mandrel is then dipped in the polyurethane solution, and is then cured at 70°C for 60 minutes. The mandrel is dipped in a second hydrophilic solution and cured at 70°C for 60 minutes. The first and second hydrophilic solutions may or may not be the same solution.

25

EXAMPLE 6:

PREPARATION OF A STENT INCLUDING SLEEVE WITH HYDROGEL INNER AND OUTER LAYERS (According to Figure 1)

30

A 18% solution of polyurethane in N,N-dimethylacetamide is prepared. Two hydrogel solutions are prepared as inner and outer layers.

The transluminal prosthesis (stent) is put onto a 2 mm mandrel.

The mandrel is dipped in a first hydrogel solution.

35

The dipped mandrel is cured at 70°C in an oven for 60 minutes.

The mandrel is then dipped in the polyurethane solution, and is then cured at 70°C for 60 minutes. The mandrel is dipped in a second hydrophilic solution and cured at 70°C for 60 minutes.

40

The stent sleeve is retrieved from the mandrel.

The transluminal prosthesis is placed onto 2-4 PTCA catheter and is inflated at the 2-4 mm diameter.

45

The advantages of the sleeves according to the invention are that they provide a sheath to improve the surface of the stent and/or to locally deliver therapeutic agent(s) to an arterial wall or lumen. The covered transluminal prosthesis can be used advantageously in a coronary artery after an angioplasty procedure but also to treat a prostate cancer whereby

50

55

5 a chemotherapeutic agent is released directly into the urethra via the
translumenal prosthesis implanted as an endoluminal prosthesis. Since a
10 sleeve according to the present invention is used for delivering the
therapeutic agent(s) and not the translumenal prosthesis itself the
5 quantities of therapeutic agent are bigger than can be achieved with a
15 coated translumenal prosthesis.

Claims

5

10

15

20

25

30

35

40

45

50

55

5

18

CLAIMS

10

15

20

25

30

35

40

45

50

55

1. A sleeve for encompassing an expandable device for introduction into a body canal, characterised in that said sleeve is multi-layered and comprises at least one biocompatible, non-biodegradable elastic polymer layer onto which one synthetic, hydrogel inner layer and/or one synthetic hydrogel outer layer is bound, said hydrogel inner layer being optionally different from said hydrogel outer layer, the nature and thickness of said biocompatible, non-biodegradable elastic layer being such that pre-determined mechanical properties of said sleeve be provided.
2. A sleeve for encompassing an expandable device for introduction into a body canal, characterised in that said sleeve is multi-layered and comprises at least one biocompatible, non-biodegradable elastic polymer layer onto which at least one synthetic therapeutic agent(s)-containing hydrogel inner layer and/or at least one synthetic therapeutic agent(s)-containing hydrogel outer layer is bound, said therapeutic agent(s)-containing hydrogel inner layer being optionally different from said therapeutic agent(s)-containing hydrogel outer layer, the nature and thickness of said biocompatible, non-biodegradable elastic polymer layer being such that predetermined mechanical properties of said sleeve be provided, and the nature and thickness of said therapeutic agent(s)-containing hydrogel inner and outer layers being such that a pre-determined rate of release of said therapeutic agent(s) be controlled.
3. The sleeve according to claim 1 or 2, characterised in that said biocompatible, non-biodegradable elastic polymer layer comprises a synthetic material selected from the group consisting of polyurethane, silicone, and latex.
4. The sleeve according to any one of claims 1 to 3, characterised in that said inner and outer synthetic hydrogel layers independently comprise at least one hydrophilic polymer selected from the group consisting of

5

10

15

20

25

30

35

40

45

50

55

polyhydroxyethyl methacrylate, polyvinyl alcohol, polyacrylamide, poly(N-vinylpyrrolidone), polyethylene oxide, hydrolysed polyacrylonitrile, polyacrylic acid, polymethacrylic acid, polyethylene amine, alginic acid, pectinic acid, carboxy methyl cellulose, and hyaluronic acid.

5. The sleeve according to any one of claims 1 to 4, characterised in that the thickness of said biocompatible, non-biodegradable elastic polymer layer is between 25 and 60 μm , preferably between 30 and 40 μm .

6. The sleeve according to any one of claims 1 to 4, characterised in that the thickness of said hydrogel inner and outer layers is, in the dry state, between 7 and 20 μm .

7. The sleeve according to any one of claims 2 to 6, characterised in that said therapeutic agent(s)-containing hydrogel inner layer contains one or more therapeutic agents capable of treating a disorder of a body fluid.

8. The sleeve according to any one of claims 2 to 7, characterised in that said therapeutic agent(s)-containing hydrogel outer layer contains one or more therapeutic agents capable of treating a disorder of a body canal wall.

9. The sleeve according to any one of claims 2 to 8, characterised in that said therapeutic agent(s) is (are) selected from the group consisting of an anticoagulant, such as D-Phe-Pro-Arg chloromethyl ketone, an RGD peptide-containing compound, heparin, an antithrombin compound, a platelet receptor antagonist, an anti-thrombin antibody, an anti-platelet receptor antibody, aspirin, a prostaglandin inhibitor, a platelet inhibitor, a tick anti-platelet peptide, or a combination thereof; a promoter of vascular cell growth, such as a growth factor stimulator, a growth factor receptor agonist, a transcriptional activator, a translational promoter, or a combination thereof; an inhibitor of vascular cell growth, such as a growth factor inhibitor, a growth factor receptor antagonist, a transcriptional repressor, a translational repressor, an antisense DNA, an antisense RNA, a replication inhibitor, an inhibitory antibody, an antibody directed against

5 growth factors, a bifunctional molecule consisting of a growth factor and a
cytotoxin, and a bifunctional molecule consisting of an antibody and a
10 cytotoxin, or a combination thereof; a cholesterol-lowering agent, a
vasodilating agent, an agent which interferes with endogenous vasoactive
5 mechanisms, or a combination thereof; or a smooth muscle inhibitor, such
as an agent which modulates intracellular calcium binding proteins, a
15 receptor blocker for contractile agonists, an inhibitor of the
sodium/hydrogen antiporter, a protease inhibitor, a nitrovasodilator, a
20 phosphodiesterase inhibitor, a phenothiazine, a growth factor receptor
10 agonist, an antimitotic agent, an immunosuppressive agent, a protein kinase
inhibitor, or a combination thereof; or a combination thereof.

25 10. A system for introduction into a body canal, characterised in that it
comprises an expandable device and a multi-layered sleeve according to
any one of claims 1 to 9.

30 11. The system according to claim 10, characterised in that said
expandable device for introduction into a body canal is embedded within
said biocompatible, non-biodegradable elastic polymer layer.

35 12. The system according to claim 10, characterised in that said
expandable device for introduction into a body canal is disposed radially
20 and internally with respect to said inner hydrogel layer.

13. The system according to any one of claims 10 to 12, characterised
in that said expandable device for introduction into a body canal is a stent.

40 14. The system according to any one of claims 10 to 13, characterised
in that it is intended to be introduced into a body canal comprising a canal
25 wall and a lumen through which a body fluid flows and in that said sleeve
comprises a therapeutic agent(s)-containing hydrogel inner layer which
45 contains one or more therapeutic agents capable of treating a disorder of
said body fluid, and a therapeutic agent(s)-containing hydrogel outer layer
50 which contains one or more therapeutic agents capable of treating a
30 disorder of said body canal wall.

5

10

15

20

25

30

35

40

45

50

55

15. A method of manufacturing a sleeve as claimed in any one of claims 1 to 9, said method comprising dipping a mandrel successively into different solutions in order to build up said layers, said dipped mandrel being subject to curing inbetween each successive dipping.

16. A method as claimed in claim 15 in which said mandrel is first dipped in a polymer solution and thence cured to form said elastic polymer layer, thence dipped into a hydrogel solution and thence cured to form a hydrogel layer.

17. A method as claimed in claim 16 wherein, in order to form said polymer layer, multiple dippings into said polymer solution, with curing inbetween, are carried out until the desired thickness for the polymer layer is achieved.

18. A method as claimed in either one of claims 16 or 17 in which, following the formation of said hydrogel layer, the sleeve is removed from the mandrel, turned inside out, and put back again onto the mandrel, following which the coated mandrel is dipped in a hydrogel solution, which may or may not be the same as the first-mentioned hydrogel solution, and is then cured.

19. A method as claimed in claim 18 wherein, after the sleeve has been replaced on the mandrel after having been turned inside out, a stent is placed over the mandrel and sleeve prior to the dipping step.

20. A method as claimed in claim 15 in which said mandrel is first dipped in a hydrogel solution and thence cured to form a hydrogel layer, is then dipped into a polymer solution and is thence cured to form a polymer layer and is then dipped into a hydrogel solution which may or may not be the same as the first-mentioned hydrogel solution, followed by curing.

21. A method as claimed in claim 20 wherein prior to the first dipping in a hydrogel solution, a stent is placed over the mandrel so that said hydrogel layer is formed over the stent and mandrel.

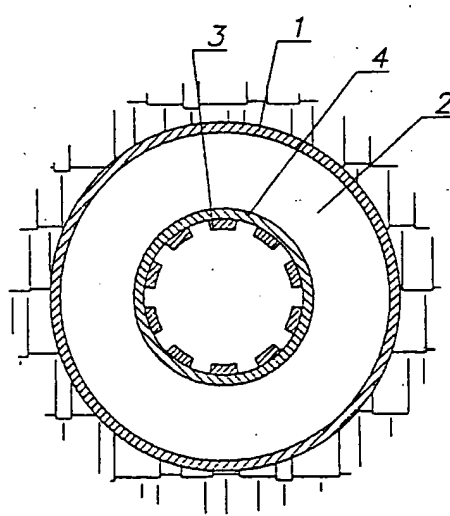
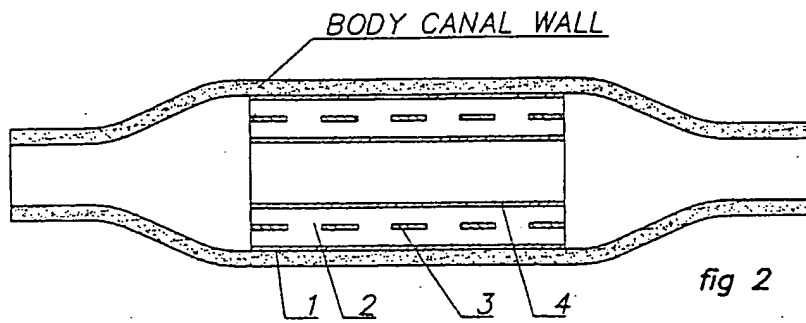
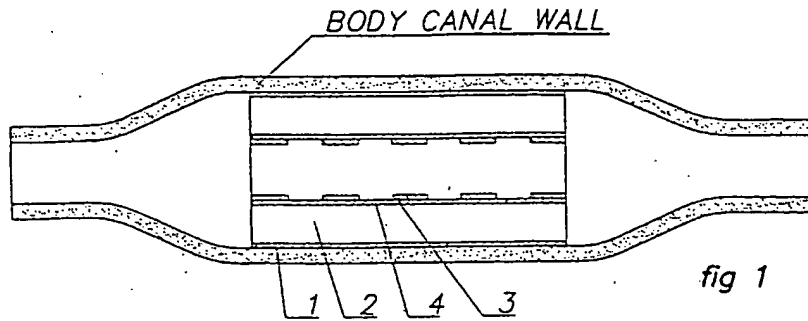


fig 1A

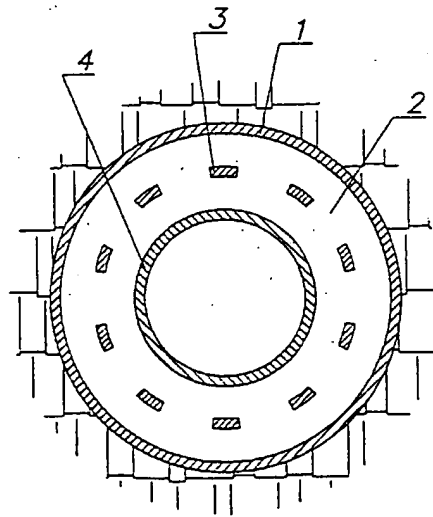


fig 2A

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/EP 99/07156

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61L29/00 A61L31/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61L B05D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 29647 A (SCIMED LIFE SYSTEMS INC) 9 November 1995 (1995-11-09)	1-13
Y	figures 6,10,12 page 4, line 26 - line 30 page 5, line 9 - line 17 page 5, line 24 - line 27 page 6, line 18 - line 26 page 7, line 16 - page 8, line 20 page 13, line 23 - page 14, line 2	15-21
X	US 5 383 928 A (SCOTT NEAL A ET AL) 24 January 1995 (1995-01-24) cited in the application column 6, line 27 - line 35 claims 1-25	1,2,5-8
--- -/--		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *A* document member of the same patent family		
Date of the actual completion of the international search 10 December 1999		Date of mailing of the international search report 21/12/1999
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3018		Authorized officer Thornton, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. J. Appl. No.

PCT/EP 99/07156

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 10989 A (SCIMED LIFE SYSTEMS INC) 27 April 1995 (1995-04-27)	15-21
A	page 6, line 19 -page 7, line 3 figures claims	1-9
A	WO 96 23602 A (SCHNEIDER USA INC) 8 August 1996 (1996-08-08) examples 1-3,5-8 claims	1-21
A	WO 98 29148 A (SCIMED LIFE SYSTEMS INC) 9 July 1998 (1998-07-09) page 4, line 1 -page 6, line 8 figures claims	1-14
A	WO 93 06792 A (SCIMED LIFE SYSTEMS INC) 15 April 1993 (1993-04-15) page 16, line 32 -page 17, line 3 page 17, line 23 - line 29 page 19, line 24 - line 28 page 22, line 10 -page 23, line 2 page 23, line 18 - line 32	1-14
A	WO 98 38947 A (SCIMED LIFE SYSTEMS INC) 11 September 1998 (1998-09-11) the whole document	1-14
A	US 5 443 458 A (EURY ROBERT P) 22 August 1995 (1995-08-22) figure 2 claims 13-25	1-14
A	US 5 304 121 A (SAHATJIAN RONALD) 19 April 1994 (1994-04-19) the whole document	1-11,13, 14
A	EP 0 604 022 A (ADVANCED CARDIOVASCULAR SYSTEM) 29 June 1994 (1994-06-29) the whole document	1-4,7-14
P,X	WO 99 44665 A (UNIV FLORIDA) 10 September 1999 (1999-09-10) claims 1,2,4-7,35,61-75 page 30, line 11 - line 31 page 6, line 34 -page 7, line 28	1-4,7-14

Form PCT/ISA-210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/07156

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9529647 A	09-11-1995	EP 0746375 A EP 0754017 A JP 9503945 T JP 10503663 T WO 9511055 A US 5693085 A	11-12-1996 22-01-1997 22-04-1997 07-04-1998 27-04-1995 02-12-1997
US 5383928 A	24-01-1995	NONE	
WO 9510989 A	27-04-1995	US 5735897 A	07-04-1998
WO 9623602 A	08-08-1996	CA 2211651 A EP 0806992 A JP 10502856 T	08-08-1996 19-11-1997 17-03-1998
WO 9829148 A	09-07-1998	EP 0956056 A	17-11-1999
WO 9306792 A	15-04-1993	US 5968092 A US 5464450 A US 5551954 A US 5500013 A US 5769883 A	19-10-1999 07-11-1995 03-09-1996 19-03-1996 23-06-1998
WO 9838947 A	11-09-1998	NONE	
US 5443458 A	22-08-1995	NONE	
US 5304121 A	19-04-1994	CA 2098984 A DE 69131486 D EP 0565604 A EP 0920843 A JP 6503984 T WO 9211896 A US 5674192 A US 5954706 A US 5843089 A WO 9211895 A	29-06-1992 02-09-1999 20-10-1993 09-06-1999 12-05-1994 23-07-1992 07-10-1997 21-09-1999 01-12-1998 23-07-1992
EP 0604022 A	29-06-1994	CA 2111455 A JP 6218063 A	23-06-1994 09-08-1994
WO 9944665 A	10-09-1999	NONE	